PATENT COOPERATION TREA

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	17 APR 2004
Applicant's or agent's file reference M80585658:JWC:KJM:CT	REPLY DUE within **TWO MONTHS** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU03/01177	9 September 2003	9 September 2002

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C12N 15/11, 15/85, A01K 67/00

Applicant
BENITEC AUSTRALIA LIMITED et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The **FINAL DATE** by which the international preliminary examination report must be established according to Rule 69.2 is:
9 January 2005

4. The applicant is hereby **invited to reply** to this opinion.

When? See the **Reply Due** date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the **Final Date** by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least **3 months before the Final Date** by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6

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WRITTEN OPINION

International application No.
PCT/AU03/01177

I. Basis of the opinion

1. With regard to the elements of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

WRITTEN OPINION

International application No.
PCT/AU03/01177

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	10, 25	YES
	Claims	1-9, 11-24, 26-40	NO
Inventive step (IS)	Claims		YES
	Claims	1-40	NO
Industrial applicability (IA)	Claims	1-40	YES
	Claims		NO

2. Citations and explanations

The following documents identified in the International Search Report have been considered for the purposes of this report:

- D1 WO A 2001/049844 (Rutgers, The State University of New Jersey) 12 July 2001
- D2 WO A 2001/077350 (Large Scale Biology Corporation) 18 October 2001
- D3 Giordano, E. et al., February 2002, Genetics, 160:637-648
- D4 Tavernarakis, N. et al., 2000, Nature Genetics, 24:180-183
- D5 Kennerdell, J.R. and Carthew, R.W., 2000, Nature Biotechnology, 18:896-898
- D6 Paddison, P. J. et al., April 2002, Genes & Development, 16:948-958

The invention defined by the present claims relates to the use of a genetic construct to produce sense-antisense sequences identical to at least a portion of a target gene in an animal cell, thereby inhibiting or reducing expression of the target gene. The genetic constructs comprise
(a) at least two copies of a nucleotide sequences substantially identical to at least a region of the target gene, one of said copies in the sense orientation, and the other in the antisense orientiation; OR
(b) one or more copies of a nucleotide sequence substantially identical to at least a region of the target gene placed between opposing first and second promoter sequences.

The invention further relates to transgenic animals that comprise these constructs, wherein expression of the target gene is reduced.

NEW CITATION

D7 WO 2001/70949 (Benitec Australia Ltd) 27 September 2001

Novelty (N) and Inventive Step (IS)

D1 discloses a method of reducing or inhibiting the expression of a target by the use of a genetic construct comprising a promoter element operably linked to a first and second coding sequence, with one sequence in the sense orientation and the other in the antisense orientation (p. 2 line 16-33), and the use of this method to produce transgenic animals (p. 9 line 22-26; p. 26 line 10-26). The first and second coding sequences range between 20 and 2500 nucleotides in length (p. 11 line 14-16), and may be separated by a spacer comprising an intronic region (p. 11 line 25-29). The citation further discloses the use of a variety of different vectors, including a viral vector, to direct expression of the dsRNA (p. 22 line 14 - p. 25 line 15). As such, the invention defined by claims 1, 2, 4-7, 9, 15, 16, 18,-20, 22-24, 28, 29, 31-39 is not novel.

Continued in Supplemental Box

WRITTEN OPINION

International application No.
PCT/AU03/01177

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 03/006477	23 January 2003	12 July 2002	12 July 2001
. WO 03/022052	20 March 2003	13 September 2002	13 September 2001
. WO 03/056012	10 July 2003	19 December 2002	24 December 2001

With regard to the document(s) listed in Box VI under "certain documents cited", these are documents published prior to the international filing date but later than the priority date claimed but which would otherwise be considered to be of particular relevance.

Under the PCT, novelty is considered only in respect of documents published before the priority date. The relevance of a document published after the priority date is dependent upon national law. Such documents are excluded from consideration in preliminary examination, under the PCT Guidelines but have been included here for information.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 40 is not clear. The scope of the term "bioactive substance" cannot be determined.

Supplemental Box I

Continuation of V (Novelty and Inventive Step)

While claims 3, 10-14, 17, 21, 25-27, 30 and 40 are novel when compared to D1, they are not considered to involve an inventive step.

Claims 3, 11, 12, 17, 21, 26, 27, 30, merely add a feature relating to the type of genetically modified animal, however the citation clearly states that any organism which may be transformed with the disclosed constructs may be produced, including mice (p. 26 line 10-18, p. 27 line 1-11), hence there is no invention in providing the claimed transgenic animals.

Furthermore, the features added by the remaining claims relate to the selection of the target gene (GalT or tyrosinase) or the cells in the animal that comprise the genetic constructs disclosed. The specification does not disclose any advantageous or unexpected properties provided by selecting these particular target genes or the cells of the animal which comprise the genetic constructs. Therefore, claims 10, 13, 14 and 25 do not involve an inventive step.

D2 describes a recombinant vector for mediating gene silencing wherein said vector allows bi-directional transcription of a transgene to yield both sense and antisense RNA transcripts (p. 11 line 19-29; Figure 2). The transgene transcribed by the vector may be an endogenous gene or heterologous gene, for example a gene derived from a pathogen (p. 16 line 31- p. 17 line 6). The citation further describes the use of said vectors to generate transgenic animals (p. 23 line 3-12). Therefore, the invention defined by claims 8, 9, 11 and 12 is not novel.

The features added by claims 10. 13 and 14 relate to the selection of the target gene or the cells in the animals that comprise the genetic constructs disclosed. The specification does not disclose any advantageous or unexpected properties provided by selecting these particular target genes or the cells of the animal which comprise the genetic constructs, therefore claims 10, 13 and 14 do not involve an inventive step. Furthermore, it would be routine for a person skilled in the art to produce progeny from the claimed transgenic animals, therefore claim 38 does not involve an inventive step.

D3 describes the use of transgenes that produce dsRNA molecules by means of sense-antisense transcription to trigger silencing of an endogenous gene in *Drosophila*. The transgenic animals described in the citation comprise a construct that produces dsRNA by symmetrical transcription (SympUAST-w) or a construct that comprises two copies of the target nucleotide sequence, one in the sense orientation and the other in the antisense orientation (Figure 3A). The citation discloses all features of the invention defined by claims 1, 2, 4, 5, 8, 9, 15, 16, 18-20, 22-24, 28, 29, 31, 35, 36, 38, 39, hence these claims are not novel.

While claims 3, 6, 7, 10-14, 17, 21, 25-27, 30, 32-34, 37, 40 are novel when compared to D3, they are not considered to involve an inventive step. The features added by these claims relate to parameters that are merely matters of design choice when the general technical knowledge about the state of the art is used and hence they cannot contribute to patentable invention.

D4 discloses genetically modified *Caenorhabditis elegans* which exhibit reduced expression of a target gene mediated by *in vivo* expression of dsRNA produced by transcription from a construct comprising an inverted repeat gene (sense and antisense copies of the target gene; Figure 1). The inverted repeat gene comprises 580 bp-1.2 kb, and is operably linked to a promoter sequence. Consequently, claims 1, 4, 5, 9, 15, 16, 22, 24, 28, 31, 35, 38 and 39 are not novel in light of D4.

Continued in Supplemental Box II

Supplemental Box II

Continuation of V (Novelty and Inventive Step)

The features added by claims 2, 3, 6, 7, 10, 11-14, 17, 18, 32-34, 40 relate to parameters that are merely matters of design choice when the general technical knowledge about the state of the art is used and hence they cannot contribute to patentable invention. Hence these claims do not involve an inventive step in light of D4.D5 describes genetically modified *Drosophila* which exhibit reduced expression of a target gene where the animal comprises a transgene having a copy of a region of the target gene in the sense orientation, a five base-pair spacer, and a second copy of the target region in the antisense orientation (Figure 2). Consequently, claims 1, 2, 4, 5, 9, 13-16, 18-20, 22-24, 28, 29, 31, 35, 36, 39 are not novel in light of D5.

D5 also states that the genetic constructs used for gene silencing may be successfully applied to silence genes in other organisms that have established transgenic technology such as mice (p. 897, right column, final sentence of second paragraph). Thus, it is considered that the citation teaches towards the use of a transgene having a copy of a region of the target gene in the sense orientation, a short spacer, and a second copy of the target region in the antisense orientation, to bring about gene silencing in vertebrate animals such as mice. As such, claims 3, 11, 12, 17, 21, 26, 27, 30, 37 do not involve an inventive step.

With regard to the claims that add features relating to the type of stuffer fragment, target gene, length of target gene or type of vector used the specification does not disclose any advantageous or unexpected properties provided by selecting the particular parameters claimed. These parameters are known in the art, hence their selection merely represents a matter of design choice. Therefore claims 6, 7 10 and 25, 32-34 do not involve an inventive step. Furthermore, claims 38 and 40 do not involve an inventive step as it would be routine for a person skilled in the art to produce the progeny of the transgenic animals defined, and to co-administer a bioactive substance with the genetic construct or vector when carrying out the methods described.

D6 teaches that short hairpin RNA can be transcribed *in vivo* and provoke effective silencing of a target gene (p. 954, left column, paragraph 3 - right column paragraph 1, Figure 4). Although the citation does not specifically disclose transgenic animals that comprise genetic constructs according the present invention, it does suggest the use of encoded short hairpins in the creation of stable mutants and the construction of transgenic animals (p. 956, right column, first paragraph). Therefore, based on the disclosure of the citation it would be obvious to use similar constructs to produce transgenic animals, hence the invention defined by claims 1-7, 9-40 does not involve an inventive step.

D7 describes methods of altering the phenotype of a vertebrate animal using a genetic construct comprising a sequence of nucleotides substantially identical to a target endogenous sequence of nucleotides in the genome of the vertebrate animal (see for example p. 12 lines 13-18). In a preferred embodiment the nucleotide sequence in the genetic construct further comprises a nucleotide sequence complementary to the target endogenous nucleotide sequences and an intron sequence (spacer) separating said nucleotide sequences (p. 14 lines 10-20). The citation describes the generation of transgenic animals using such genetic constructs (Example 15, 16), wherein the target gene is GalT or tyrosinase. As such the citation discloses all features of the invention defined by claims 1-6, 9-31, 35-37, 39, hence these claims are not novel. Furthermore, the features added by claims 7, 32-34, 40 merely relate to the choice of alternatives that are known in the art. As such these claims do not involve an inventive step.